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Vestibular Reflexes of Otolith Origin
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Introduction

This grant provided partial support for three projects, which are described below in summary form. Underlying all the projects, which were carried out on cats, was an interest in the vestibular system and its role in the maintenance of posture and in motion sickness. The assumption has been, and remains, that better understanding of the physiology of vestibular pathways is not only of intrinsic value, but will help to explain and eventually alleviate the disturbances caused by vestibular malfunction, or by exposure to an unusual environment such as space. The first project dealt with the influence on the spinal cord of stimulation of the vestibular labyrinth, particularly the otoliths. The second was concerned with the properties and neural basis of the tonic neck reflex. These two projects are related, because vestibulospinal and tonic neck reflexes interact in the maintenance of normal posture. The third project began with an interest in mechanisms of motion sickness, and eventually shifted to a study of central control of respiratory muscles involved in vomiting.

A list of all the papers describing work supported by this grant concludes the report. These papers will be referred to by number at appropriate places in the text.

A. Otolith reflexes acting on the limbs.

The analysis of the otolith-spinal system began with a study of reflexes evoked in cat forelimb extensor muscles by sinusoidal roll tilt of animals whose semicircular canals were inactivated (1). This revealed that otolith reflexes had unusual dynamics, particularly a large phase lag that developed at frequencies over 0.1 Hz. Such responses were also found in some neurons in the lateral vestibular nucleus particularly those excited by downward tilt of the contralateral ear (4). This was important, because this nucleus sends all of its axons to the spinal cord. Lesions of the spinal cord then revealed that hemisection affected the dynamics of reflexes in the contralateral limb (5). At this stage experiments had revealed reflex dynamics, and suggested that an important neural substrate was a pathway crossing in the spinal cord. The next step was to move away from simple roll, or pitch, stimulation and to determine whether central neurons or muscles had preferred directions of tilt. This was done by developing a stimulus which combined roll and pitch (11). It was then found that most neurons in Deiters' nucleus were excited by a tilt direction closer to roll than to pitch. This response vector orientation is not changed by stimulus frequency (18). Recent observations have shown that response vectors of neurons in this nucleus behave similarly in animals with functioning canals (36). Modeling of neuron response suggests that the behavior of neurons responding to contralateral ear down tilt with a phase lag at higher frequencies can be explained by a gain element in parallel with an inhibitory high-pass filtered version of the input (17,18). This inhibitory pathway could be in the cerebellum. Studies turned next to response vector orientations of various forelimb extensor

muscles. It was shown that these vector orientations are even closer to roll than those of vestibular neurons (24). This was so even though these animals had functioning semicircular canals, and the dynamics of muscle responses clearly showed combined otolith and canal input. In this respect muscle responses behave like vestibular nucleus neurons, as referred to above (36). Earlier work had strongly suggested that vestibulospinal neurons acted on forelimb motoneurons via spinal interneurons. We therefore looked at responses of interneurons in the cervical cord to our usual stimuli (26). As expected, these neurons responded preferentially to roll. In labyrinth-intact cats, their dynamics resembled those of both vestibular neurons and muscles. In cats with canals inactivated, however, few phase lagging responses were found in interneurons.

Our experiments have provided considerable insight into the behavior of vestibular neurons, spinal neurons, and forelimb extensor muscles to stimulation of both otoliths and canals. An important link in the pathway from vestibular neurons to motoneurons remains to be identified. That vestibulospinal reflexes of the forelimbs are more readily evoked by roll than pitch stimuli may be because a standing quadruped is much more stable around a pitch than a roll axis of tilt.

B. Reflexes evoked by neck afferents: the tonic neck reflex.

That signals originating in neck afferents are important in the maintenance of normal posture has been known for a long time, but until recently they had not been studied systematically. We turned to the tonic neck reflex acting on the forelimbs because of its interaction with vestibulospinal reflexes, and because this reflex appeared to be a good

model for the study of a simple motor behavior. The first experiments used sinusoidal roll stimulation of neck receptors to study reflex dynamics (9). Over a broad frequency range the reflex EMG was in phase with position. Modest gain increase and phase advance above 0.2 Hz showed some sensitivity to stimulus velocity. As expected from previous work of others, vestibulospinal and tonic neck reflexes were opposite in polarity and could cancel (13). More recent experiments show that this holds true for responses to multidimensional stimuli (24). A substantial effort was devoted to identifying spinal neurons in the reflex pathway. The first studies in the cervical cord revealed interneurons at mid cervical levels and in the cervical enlargement that had dynamics similar to reflex dynamics (12). Neurons often responded to vestibular stimulation, and as in muscle, neck and vestibular responses opposed each other, often to the point of cancellation. We then used methods developed in the vestibular project to study vector orientations of responses to neck stimulation in lumbar neurons (14,19). Vector orientations covered a wide range. Again, many neurons responded to both neck and vestibular stimuli: when they did, response vector orientations were approximately opposite in direction. Many of the interneurons, in the mid-cervical and mid-lumbar cord, were propriospinal neurons whose axons extended to the respective enlargements (23). Presumably these propriospinal neurons transmit neck signals to motoneurons, but whether they do so directly or via more interneurons is not yet known. Neck-vestibular interaction has also been looked at in the vestibular nuclei, specifically the lateral and rostral descending nuclei which both send fiber tracts to the spinal cord (37). The main result of this study is that neurons with otolith, canal, or otolith + canal input

may get neck input. Neck and vestibular response dynamics are often similar, and, particularly in the case of otolith neurons, simultaneous activation of neck and vestibular receptors often elicits no response (cancellation). Neurons that function in this way have the properties to be in vestibular and neck reflex pathways to the limbs.

Having established the properties and, in part, the pathway from neck receptors to spinal motoneurons, and having studied neck-vestibular interaction in detail at different loci, we went in two different directions. In the first, we studied peripheral input from limb nerves to lumbar neurons modulated by neck rotation (34). So far we have shown that such input is prominent from cutaneous nerves, and that some neurons receive input from secondary spindle receptors from knee extensor muscles. These latter neurons, and others lacking this muscle input, may belong to two functionally different populations. The other experiments addressed the question: what are the receptors for the tonic neck reflex? Old evidence suggested a primary role for neck joint receptors, but more recent work suggested a role for the numerous spindles in neck muscles. We have recorded from many spindle afferents in the C2 dorsal root ganglion (28,33). They respond to sinusoidal neck rotation very similarly to spinal interneurons, and their axons project to areas where the mid-cervical propriospinal neurons are found. It is therefore extremely likely that afferents for the tonic neck reflex originate, at least in part, from muscle spindles in the neck.

We have also looked at the projection of neck muscle afferents to neck motoneurons (3,8). These muscles, which are subdivided anatomically, are innervated by several segmental ganglia. The results show that spindle

afferents from each segmental level preferentially innervate part of the muscle, providing a basis for localization of stretch reflexes.

C. Studies on motion sickness and vomiting.

Initial studies re-examined the role of certain central nervous system structures in the production of vestibular-induced vomiting and vomiting in general. All experiments were conducted using cats. Vomiting and related prodromal activity were produced after ablation of the nodulus and uvula of the vestibulocerebellum by using sinusoidal electrical stimulation of the vestibular labyrinths of decerebrate animals to mimic natural vestibular stimulation (10). The nodulus and uvula, therefore, are not an essential part of the mechanism(s) by which vestibular input can activate brain stem structures responsible for vomiting. We were also unable to confirm the existence of an anatomically well defined brain stem "vomiting center" in other studies that used electrical microstimulation of the brain stem in an attempt to elicit vomiting (7).

Since these studies demonstrated that the essential role of various central structures in vestibular-induced vomiting is only poorly understood, efforts were re-directed to study the control of the effector muscles (diaphragm and abdominal muscles) that produce the pressure changes responsible for vomiting, with the goal of determining how this control mechanism is engaged during motion sickness. Experiments were conducted to localize the motoneurons that innervate the individual abdominal muscles (30) and the portion of the diaphragm that surround the esophagus (27). In contrast to the rest of the diaphragm, the periesophageal region relaxes during expulsion, thereby facilitating rostral movement of gastric

contents. In order to study the role of individual brain stem neurons in the control of the diaphragm and abdominal muscles during vomiting, a "fictive vomiting" preparation was developed using paralyzed, decerebrate animals (31). Fictive vomiting was defined by a characteristic pattern of co-activation of abdominal and phrenic nerves, elicited by emetic agents, that would be expected to produce vomiting in unparalyzed animals. A central question regarding respiratory muscle control during vomiting is whether these muscles are activated via the same brain stem pre-motor neurons that provide descending respiratory drive and/or by other descending input(s). This question was addressed in regard to expiratory neurons in the caudal ventral respiratory group (VRG). There is a large projection from these neurons to the thoracic and lumbar cord, from which the abdominal muscles receive their innervation; however, cross-correlation analysis indicated that there are few strong monosynaptic connections between these neurons and abdominal motoneurons (22). Some VRG expiratory neurons have the appropriate firing pattern during fictive vomiting to contribute to abdominal muscle control; however, other as yet unidentified inputs can also produce abdominal muscle activation during vomiting as was shown by severing the axons of VRG expiratory neurons (31).

In other experiments, we evaluated the use of a combination of pitch and roll motions to produce motion sickness in unrestrained cats. This stimulus combination can produce vomiting in only the most susceptible cats and is thus not as provocative a stimulus for cats as vertical linear acceleration, which has been used by other investigators.

In addition to the papers referred to in the text, there were other

publications resulting from reports at international meetings (2,15,16,20, 21,29,32,35).

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